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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,317	10/15/2003	Susan M. Freier	IBIS0009-101 (ISPH-0794)	8250

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,317	FREIER ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11,17-22 and 25-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,17-22 and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I, claims 1-14, 17-22 and 25-29 in the reply filed on June 15, 2005 is acknowledged. Applicant requests reconsideration of the burden placed on the Examiner in examining more than one group. These arguments are moot in view of Applicant's cancellation of all claims directed to the non-elected inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10, 12-16, 23, 24, 30 and 31 have been canceled. Claims 1-9, 11, 17-22 and 25-29, all directed to the invention of group I, are currently pending and examined on the merits.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
The declaration of inventor Giddings is unsigned.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 1 recites at lines 5-7 that each of the antisense oligonucleotide sequences "has an experimentally determined capacity to inhibit expression of its complementary nucleic acid target". The metes and bounds of this limitation are unclear. For example, does this step include oligonucleotide sequences that have a capacity to inhibit but do not under the conditions that may be used/selected for the instant method have a capacity to inhibit a target? (See for example, Stewart et al., where ISIS 7607 and ISIS 7608 have the same sequence but different modifications that affect their capacity to inhibit? Or, for example, antisense capacity as determined in cell free systems vs. cells in culture vs. in vivo?) Further, it is unclear what is embraced by the limitation "its complementary nucleic acid target". The specification provides definitions of targets at page 8, but does not provide a definition of "complementary nucleic acid target". Does this target include arbitrary sequences, mRNA sequences, gene sequences, etc? The first step of claim 1 is unclear. The method step comprises subdividing each of the antisense oligonucleotide sequences into subsequences of defined length. The claim as written can be interpreted in several ways, which include, for example, the method performed physically or by data analysis. In view of this it is unclear how a sequence per se has a capacity to inhibit. Further, are the sequences being subdivided or are oligonucleotides being subdivided by length? For example, is each individual oligonucleotide or oligonucleotide sequence subdivided into defined lengths or is the set of oligonucleotides subdivided based on oligonucleotide lengths? The final step of

claim 1 is also unclear. For example, the step includes eliminating the motifs whose correlation with antisense activity is unique to a particular target. Does this include an oligonucleotide sequence that is specific for a particular target? How is this uniqueness determined? Unique to what particular sequence?

2. The second step of claim 1 refers to significant correlation. What is one in the art to use to determine what is significant and what is to be considered significant in the instant method?

3. Claim 1 is also unclear since it does not include a conclusion that relates back to the preamble of the claim.

4. In claim 7 it is unclear what one would consider to be a "desired threshold of significance".

5. Claim 9 contains the same concerns as claims 1 and 7 above.

6. In considering the art applied below the designation of "activity-enhancing/decreasing motifs" has been generally interpreted to be any sequence in a particular antisense that causes that antisense to be active or inactive. An active antisense that may comprise those motifs in the instant specification designated as activity-decreasing are considered not to have such a motif in view of the fact that it is unclear under what conditions the designations (see rejection under 35 usc 112, second paragraph above) of the instant application were determined and since the antisense oligonucleotides applied as art indeed have antisense activity. The Stewart reference, for example provides a list of active antisense oligonucleotides. All of the active antisense oligonucleotides contain motifs that the instant application designates as

enhancing and further all of the active antisense, including the most active, contain motifs disclosed in the instant application as activity-decreasing.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17-22 and 25-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al. (Biochemical Pharmacology, 1996, vol. 51, pages 461-469).

7. Claims 17 and 20 are directed to methods of selecting an effective antisense oligonucleotide sequence or an effective antisense target sequence, respectively, by selecting, from a set of antisense oligonucleotide sequences or target regions, those that comprise at least one activity-enhancing sequence motif. Claims 18 and 19 limit claim 17 and claims 21 and 22 limit claim 20 by stating the antisense or target sequences do not contain activity-decreasing motifs or do contain multiple activity-enhancing motifs. Claim 25 is directed to a method of designing an antisense oligonucleotide with enhanced likelihood of inhibiting expression of a target sequence by targeting the antisense to a target region comprising one or more activity-enhancing target sequence motifs. Claims 26 and 27 limit claim 25 by stating the antisense sequences do not contain activity-decreasing motifs or do contain multiple activity-

enhancing motifs. Claim 28 is directed to a method of designing an antisense oligonucleotide with enhanced likelihood of inhibiting expression of a target sequence by targeting the antisense to a target region that does not comprise any activity-decreasing target sequence motifs. Claim 29 limits claim 28 by stating the antisense sequences contains one or more activity-enhancing motifs.

8. Stewart et al. disclose providing a set of antisense oligonucleotides where the most effective antisense oligonucleotides (which contain at least one activity-enhancing oligonucleotide sequence motif where an antisense-enhancing sequence motif has been considered as any motif that causes enhanced activity such as the sequence per se and also those sequence motifs disclosed in the instant application as activity enhancing motifs and further the most effective sequence disclosed by Stewart et al. is not considered to have an activity decreasing motif since this oligo, ISIS 7597, appears to have enhanced activity). Claim 20 is rejected since once one selects an active antisense for a specific target they have inherently selected a target sequence for that specific antisense as well. See table 1, for example.

9. Thus, Stewart et al. disclose and anticipate claims 17-22 and 25-29.

Claims 25-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Robinson et al. (US 5,661,135).

10. Claims 25-29 are described in the previous 102 rejection. Robinson et al. disclose the selection of antisense oligonucleotides to inhibit VEGF. Since the antisense oligonucleotides disclosed by Robinson et al. in claim 1 for example are all active oligonucleotides they are considered not to have activity-decreasing sequences.

The sequences disclosed by Robinson also have sequences that have been designated in the instant application as "activity-enhancing" motifs. Further, SEQ ID NO: 18 does not have any of the motifs that are disclosed in the instant application to have " activity-decreasing" motifs. Robinson et al. also disclose the targeting to start and stop codon sequences which have been designated in the instant application as desirable target sequences (see page 10, for example).

11. Thus, Robinson et al. disclose and anticipate claims 25-29.

Claims 1-3, 5 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Smetsers et al. (Antisense and Nucleic Acid Drug Development 1996, vol. 6, pages 63-67).

12. Claim 1 is directed to a method of identifying an oligonucleotide sequence motif that is correlated with antisense activity by subdividing a set of antisense oligonucleotides into subsequences of defined length that are that are motifs, determining which motifs correlate with antisense activity and eliminating those motifs whose correlation is unique to a particular target. Claims 2-3 limit claim 1 by stating the length of sequence motifs. Claim 5 recites the additional step of selecting the antisense activity probability to the motif content of each oligonucleotide while claim 7 recites the additional step of eliminating motifs below a desired statistical threshold.

13. Smetsers et al. disclose a method of determining sequence motifs that are correlated with antisense activity. The method includes the steps of providing a set of antisense oligonucleotide sequences that have been shown to have antisense activity and then providing a subset of motifs within those sequences that are over represented

in active antisense sequences compared to the corresponding sequences represented in mRNA sequences. Smetsers et al. eliminated motifs that are associated with the Kozack sequence motif. See table 1 for example.

14. Thus, Smetsers et al. disclose and anticipate claims 1-3, 5 and 7.

Claims 25, 26, 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Tu et al. (WO 99/01139, cited on IDS).

15. Claims 25, 26, 28 and 29 are described in the 102 rejection over Stewart et al. Tu et al. disclose a method of selecting effective antisense via the selection of an antisense directed to TNFα, for example, that comprise a TCCC motif and further selecting target sites that include a GGGA motif and disclose antisense that contain a TCCC motif and target sites that comprise a GGGA motif. Antisense oligonucleotides disclosed by Tu et al. include antisense oligonucleotides that do not contain "activity-decreasing motifs and disclose antisense oligonucleotides that contain activity-enhancing motifs. See the claims for example.

16. Thus, Tu et al. disclose and anticipate claims 25, 25, 28 and 29.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4, 6, 8, 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smetsers et al. as applied to claims 1-3, 5 and 7 above, and further in view of the following reasons.

17. Claims 1-3, 5 and 7 are described in the previous 102 rejection under Smetsers et al. Claims 4, 6 and 8 depend from claims 1, 5 or 7 and recite use of particular methods of statistical analysis. Claim 9 is directed to a method of identifying sequence motifs predictive of antisense activity that combines the elements of claims 1, 2, and 4-8 together. Claim 11 limits claim 9 by reciting the identical limitation of claim 3.

18. The teachings of Smetsers et al. are set forth in a previous 102 rejection. The difference between the instant invention and that taught by Smetsers et al. is in the use of specific methods of data (statistical) analysis. The use of different statistic methods is a routine choice made by one in the art for the data that is to be analyzed. The specific limitations do not appear to be the patentable aspects of Applicant's invention and one in the art would have been motivated to choose various means of statistical

analysis based on various factors such as one's familiarity with a specific method of analysis or for example, to determine a desired threshold of probability. The means used to determine probabilities, for example do not change the data found by the methods of the invention. In the absence of evidence to the contrary these limitations do not define over the prior art. One of ordinary skill in the art would have had a reasonable expectation of success in using the recited methods of statistical analysis because each of these methods is well-known and routinely used for statistical analysis of data.

19. Thus, the invention of claims 4, 6, 8, 9 and 11 would have been obvious as a whole to one of ordinary skill in the art at the time the invention was made.

Claims 17, 18, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tu et al. (WO 99/01139).

20. The claimed invention is drawn to the selection of an effective antisense oligonucleotide for a desired target via the selection from a set of oligonucleotides of a desired length targeted to the desired target oligonucleotides that comprises at least one activity enhancing oligonucleotide sequence motif. The invention also includes a methods of selecting an effective antisense oligonucleotide target via selecting targets of a desired length that comprise an activity enhancing target sequence motif.

21. Tu et al. have taught the selection of effective antisense oligonucleotides via selection for antisense oligonucleotides that comprise a motif TCCC (see claims 19 and 20 and page 18 for example) and selection of targets that comprise the motif GGGA (see claim 7 and page 18 for example). The methods taught by Tu et al. do not

specifically assert selecting such oligonucleotides/targets of a specific length, however it is clear from the teaching of Tu et al. at page 8 for example that specific oligonucleotide lengths are preferred.

22. It would have been obvious to one of ordinary skill in the art at the time of invention to use a beginning set of oligos that were of a specific length since Tu et al. have taught that specific sizes of oligonucleotides are preferred and especially since it is asserted that these oligonucleotides comprise their desired motifs. Since the selection of an effective antisense oligonucleotide indicates the identification of an effective target it would further have been obvious to one in the art that the selection of an effective antisense includes the selection of an effective target.

23. Thus, the invention of claims 17, 18, 20 and 21 as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made (activity-decreasing motifs are interpreted as per paragraph 6 of the instant Office Action in this rejection).

Claims 17-22 and 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tu et al. as applied to claims 17, 18, 20 and 21 above, and further in view of Smetsers et al.

24. The claimed invention is drawn to the selection of an effective antisense oligonucleotide for a desired target via the selection from a set of oligonucleotides of a desired length targeted to the desired target oligonucleotides that comprises at least one activity enhancing oligonucleotide sequence motif. The invention also includes a method of selecting an effective antisense oligonucleotide target via selecting targets of

a desired length that comprise an activity enhancing target sequence motif. The difference the instantly rejected invention in regard to the Tu et al. rejection above is the inclusion of more than one activity enhancing motif and the inclusion of the instant specification asserted "activity-decreasing" motifs as specific limitations (see paragraph 6 of the instant Office Action).

25. Tu et al. have taught the selection of effective antisense oligonucleotides via selection for antisense oligonucleotides that comprise a motif TCCC (see claims 19 and 20 and page 18 for example) and selection of targets that comprise the motif GGGA (see claim 7 and page 18 for example). The methods taught by Tu et al. do not specifically assert selecting such oligonucleotides/targets of a specific length, however it is clear from the teaching of Tu et al. at page 8 for example that specific oligonucleotide lengths are preferred. It would have been obvious to one in the art to use a beginning set of oligos that were of a specific length since Tu et al. have taught that specific sizes of oligonucleotides are preferred and especially since it is asserted that these oligonucleotides comprise their desired motifs. Since the selection of an effective antisense oligonucleotide indicates the identification of an effective target it would further have been obvious to one in the art that the selection of an effective antisense includes the selection of an effective target.

26. Smetsers et al. have taught a method of determining sequence motifs that are correlated with antisense activity. The method includes the steps of providing a set of antisense oligonucleotide sequences that have been shown to have antisense activity and then providing a subset of motifs within those sequences that are over represented in active antisense sequences compared to the corresponding sequences represented

in mRNA sequences. Table 1 for example has provided one in the art numerous sequence motifs that have been identified as highly correlated to antisense activity and have also shown sequences that are under represented in antisense oligonucleotides.

27. It would have been obvious for one of ordinary skill in the art to supplement the teachings of Tu et al. who have taught the selection of antisense oligonucleotides and targets based on motifs that have been demonstrated to be correlated with increased antisense efficacy with the teachings of Smetsers et al. who have provided additional sequence motifs associated with antisense activity. One of ordinary skill in the art would have recognized based on these teachings that certain sequences are desirable in antisense oligonucleotides and others are not (such as those motifs under-represented in active antisense and also those taught by Smetsers et al. such as CG and GGG and GGGG that have other than "antisense" properties such as immune stimulation and protein binding). One in the art would clearly have recognized the importance of these sequence motifs and would avoid those motifs that may interfere in certain antisense applications (such as protein binding) and would have recognized on the teachings of Smetsers et al. that antisense oligonucleotides that contain more than one motif associated with antisense activity would likely be an effective antisense oligonucleotide. One of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Tu et al. and Smetsers et al. because each of these references provides teachings of antisense oligonucleotide and target sequence motifs that are actually correlated with increased antisense efficacy and motifs that are undesirable because of effects not associated with antisense activity.

28. Thus, the invention of claims 17-22 and 25-29 would have been obvious, as a whole, at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811.

On July 15, 2005, the Central FAX Number was changed to 571-273-8300. Faxes sent to the old number (703-872-9306) will be routed to the new number until September 15, 2005.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
August 9, 2005

SEAN McGARRY
PRIMARY EXAMINER